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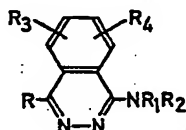
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(54) AMINOPHTHALAZINES AND PHARMACEUTICAL  
 COMPOSITIONS THEREOF

(71) We, ASPRO - NICHOLAS  
 LIMITED, a British company, of 16  
 Berkley Street, London W.1., England, do  
 hereby declare the invention, for which we  
 pray that a patent may be granted to us,  
 and the method by which it is to be per-  
 formed, to be particularly described in and  
 by the following statement:—

This invention relates to pharmacologically  
 active phthalazines, to a method for their  
 preparation, to pharmaceutical compositions  
 containing them and to a method of treat-  
 ment involving their use.

The phthalazines of the present invention  
 are represented by the formula:—



I

and an acid addition salts and quaternary  
 ammonium derivatives thereof wherein

R represents aryl or aralkyl;  
 R<sub>1</sub> and R<sub>2</sub>, which may be the same or  
 different, represent hydrogen; cycloalkyl; or  
 cycloalkyl-alkyl; provided that both R<sub>1</sub> and  
 R<sub>2</sub> are not hydrogen; or

R<sub>1</sub> and R<sub>2</sub> separately represent the same or  
 different heterocyclic or heterocyclic-alkyl or,  
 together with the adjacent nitrogen, represent  
 heterocyclic, the said heterocyclic groups  
 being rings of 5 to 7 atoms at least one of

which atoms is carbon, and at least one and  
 optionally up to four of which atoms are  
 hetero atoms selected from nitrogen, oxygen  
 and sulphur; and

R<sub>3</sub> and R<sub>4</sub>, which may be the same or  
 different, represent hydrogen; halogen;  
 cyano; hydroxy; nitro; amino; alkylamino;  
 cyano; carboxy; carboxyamino; alkyl; alkylcarbonyl;  
 alkoxy; alkoxy-carbonyl; hydroxy alkyl;  
 halogenoalkyl; or alkyl- or aryl-thio,  
 -sulphinyl or -sulphonyl.

The aforementioned heterocyclic rings  
 may be unsubstituted or substituted by  
 alkyl; hydroxyalkyl; halogenoalkyl; aryl;  
 aralkyl; carboxyalkyl; alkoxy- or aralkoxy-  
 alkyl; alkoxy- or aralkoxy-carbonyl; alkoxy-  
 or aralkoxy-carbonalkyl; alkyl- or aryl-  
 sulphonyloxyalkyl; aminoalkyl; alkylamino-  
 alkyl; acyl; acyl- or acyloxy-alkyl; or by a  
 further heterocyclic or heterocyclic-alkyl  
 group, the heterocyclic rings of which have  
 5 to 7 atoms, one or two of which are  
 heteroatoms selected from nitrogen, oxygen  
 or sulphur and the remainder of which ring  
 atoms are carbon, which rings are themselves  
 optionally substituted by alkyl, hydroxyalkyl  
 or halogenoalkyl.

By "aryl" as used herein we mean to  
 include phenyl and phenyl substituted by one  
 or more of the same or different halogen;  
 cyano; hydroxy; nitro; amino; alkylamino;  
 cyano; carboxy; carboxyamido; alkyl; alkylcarbonyl;  
 alkoxy; alkoxy-carbonyl; hydroxyalkyl;  
 halogenoalkyl; or alkyl-, phenyl- or alkyl-  
 phenyl-thio, -sulphinyl or -sulphonyl.

By "alkyl" as used herein whether

[Price 25p]



explicitly (except in the term cycloalkyl) or implicitly as in, for example, acyl (i.e. alkyl-carbonyl), we mean to include straight and branched chain radicals of up to 12 carbons which are saturated or unsaturated by one or more double or triple bonds.

Examples of suitable heterocyclic and heterocyclicalkyl and, subject to the restrictions in the definition above, heterocyclic-substituted heterocyclic radicals are imidazolidinyl, imidazolyl, pyrazolidinyl, pyrazolyl, piperidyl, picolyl, pyridylethyl, homopiperidyl, thiazolyl, thiazolyl, homopiperazinyl, homomorpholinyl, piperazinyl, morpholinyl, morpholinylpropyl, thiazinyl, thiazolidinyl, pyrrolyl, imidazolyl, pyrazolyl, pyrrolidinyl, piperidinyl, pyrrolinyl, piperidyl-methyl, morpholinylethyl, 4 - methylpiperazinyl, 2 - phenylpiperidyl, 3 - aminomethylpyrrolidinyl, 3 - chloroethylpiperidyl, 3 - hydroxypyrrolidinyl, 2 - methoxyethylmorpholinyl, 4 - phenylpiperazinyl, 0 - tolylpiperazinyl, triazolyl, tetrazolyl, oxadiazolyl, thienyl, hydroxyethylpiperazinyl, acetoxylethylpiperazinyl, 4 - picolylpiperazinyl, methylsulphonyloxyethylpyrazolyl and piperidinylpropylpiperidinyl.

Examples of suitable aryl and aralkyl radicals include phenyl, tolyl, xylyl, cumenyl, 2,3 - dimethoxyphenyl, chlorophenyl, 2,4 - dibromophenyl, cyanophenyl, hydroxyphenyl, methylthiophenyl, 4 - (o - tolylsulphonyl)phenyl, benzyl, styryl, phenethyl, 2,3 - xylylmethyl, 3 - ethylsulphonylphenyl, 2,4 - dimethoxybenzyl, 2,3,6 - trichlorobenzyl,  $\gamma$  - phenylpropyl, 4 - (o - tolyl)butyl, 2 - (2',4' - dimethoxyphenyl) ether, 1 - methyl - 2 - phenylethyl, 3 - fluorophenylalkyl, 2 - methyl - 3 - phenylpropyl, 3 - phenylprop - 2 - ynyl, 2 - chloro - 3,5 - dimethylphenyl and 2 - benzylbut - 1 - enyl.

Examples of suitable alkyl radicals are methyl, ethyl, propyl, butyl, amyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, ethenyl, ethynyl, prop - 1 - enyl, prop - 2 - enyl, (i.e. allyl), prop - 1 - ynyl, prop - 2 - ynyl (i.e. propargyl), but - 1 - enyl, but - 1 - ynyl, but - 2 - enyl, but - 2 - ynyl, but - 3 - enyl, pent - 1 - enyl, pent - 2 - enyl, pent - 2 - ynyl, pent - 4 - ynyl, 2 - methylbut - 1 - enyl, 3 - methylbut - 1 - ynyl, 2 - methylbut - 2 - enyl, and 1,1 - dimethylprop - 2 - enyl.

Examples of suitable cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

A particular preferred group of compounds of formula I are those in which

R represents phenyl or phenyl-lower alkyl (the phenyl or phenyl moiety of which is optionally substituted by halogen; cyano; hydroxy; nitro; amino; lower alkylamino; lower alkyl; lower alkylcarbonyl; lower alkoxy; lower alkoxy-carbonyl; hydroxy lower

alkyl; halogeno lower alkyl; or lower alkylthio, -sulphinyl or -sulphonyl);

R<sub>2</sub> and R<sub>3</sub>, which may be the same or different represent hydrogen; halogen; cyano; hydroxy; nitro; amino; lower alkylomino; lower alkyl; lower alkylcarbonyl; lower alkoxy; lower alkoxy-carbonyl; hydroxy lower alkyl; halogeno lower alkyl; or lower alkylthio, -sulphinyl or -sulphonyl;

R<sub>1</sub> represents hydrogen;

R<sub>2</sub> represents cycloalkyl or cycloalkyl-lower alkyl (the cycloalkyl or cycloalkyl moiety of which has 3 to 6 carbons); or heterocyclic or heterocyclic-lower alkyl; or

R<sub>1</sub> and R<sub>2</sub>, together with the adjacent nitrogen, represent a heterocyclic ring; the heterocyclic rings represented by R<sub>2</sub>, or R<sub>1</sub> and R<sub>2</sub> together, having from 5 to 6 ring atoms, at least one of which is carbon and at least one, optionally up to 4, of which

atoms are heteroatoms selected from nitrogen, oxygen or sulphur, which heterocyclic rings

are optionally substituted by lower alkyl; hydroxy- or halogeno-lower alkyl, phenyl; phenyl(lower) alkyl; carboxy(lower)alkyl;

lower alkoxy- or phenyl(lower) alkoxy-lower alkyl; lower alkoxy-carbonyl or -carbonyl-

(lower) alkyl; lower alkyl- or phenylsulphonyloxy(lower)alkyl; amino(lower)alkyl; lower alkylamino(lower)alkyl; lower acyl;

lower acyl- or lower acyloxy-lower alkyl; or by a further heterocyclic or heterocyclic-lower alkyl group, the further heterocyclic rings

having from 5 to 6 ring atoms, one or two of which are heteroatoms selected from

nitrogen, oxygen or sulphur and the remainder of which ring atoms are carbon, which further rings are optionally substituted

by lower alkyl, hydroxy- or halogeno-lower alkyl, the phenyl substituents or the phenyl moiety of substituents on the aforementioned

heterocyclic rings being optionally substituted by halogen, cyano, hydroxy, amino, lower

alkylamino, lower alkyl or lower alkoxy.

Within the aforementioned preferred group of compounds, particularly useful pharmacological properties are to be found in compounds of formula I in which R<sub>2</sub> and R<sub>3</sub>,

which may be the same or different, represent hydrogen or halogen;

R represents phenyl or benzyl, the phenyl or phenyl moiety of which is optionally substituted by halogen, cyano, hydroxy, amino, alkylamino, alkyl, alkoxy or alkylthio (the

alkyl or alkoxy moieties of which groups have 1 to 4 carbons); and either

R<sub>1</sub> represents hydrogen and R<sub>2</sub> represents cycloalkyl of 3 to 6 carbon heterocyclic or heterocyclic-lower alkyl, or

R<sub>1</sub> and R<sub>2</sub>, together with the adjacent nitrogen, represent a heterocyclic ring;

the heterocyclic rings of R<sub>2</sub>, or R<sub>1</sub> and R<sub>2</sub> together, having from 5 to 6 ring atoms up to two of which are nitrogen, up to one

of which is oxygen, and the remainder of

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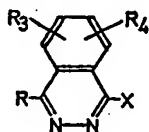
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which are carbon, which heterocyclic rings are optionally substituted by alkyl, hydroxy-alkyl or halogenoalkyl of 1 to 4 carbons; phenyl or benzyl; methoxy- or ethoxy-carbonyl, -carbonylmethyl or -carbonyl ethyl; acetyl, or propionyl; acetyl-, propionyl-, acetyloxy- or propionyloxy- methyl or -ethyl; or by a further heterocyclic or heterocyclic-methyl, ethyl, propyl or butyl, the further heterocyclic rings having from 5 to 6 ring atoms, up to two of which are nitrogen, up to one of which is oxygen and the remainder of which are carbon, which further rings are optionally substituted by alkyl, hydroxy-alkyl or halogenoalkyl of 1 to 4 carbons, the phenyl substituents or the phenyl moiety of substituents on the heterocyclic rings being optionally substituted by halogen; hydroxy; methyl; ethyl; methoxy or ethoxy.

Where in this specification reference is made to a substituent without reference to its isomeric state, that substituent includes all its isomers, e.g. reference to butyl includes *n*-butyl, iso-butyl, *s*-butyl and *t*-butyl.

The term "lower" in qualifying various groups is used herein to mean those groups containing up to 6 carbon atoms.

According to a feature of the present invention, there is provided a process for preparing the phthalazines of the present invention which comprises reacting a compound of the formula:—



II

wherein  $R_3$  and  $R_4$  are as defined in formula I and X represents halogen, or alkyl- or aryl-thio, -sulphinyl or -sulphonyl; with an amine, or an acid salt thereof, of the formula:—



wherein  $R_1$  and  $R_2$  are as defined in formula I.

The reaction may be carried out in the presence or absence of a solvent and normally will be carried out at elevated temperatures. When a solvent is used, the reaction is conveniently carried at the reflux temperature of the reaction mixture. Reaction times may vary for example from about 1 to 24 hours depending on the reaction conditions. When a solvent is used, suitable solvents include benzene, chloroform, toluene, acetone dioxan, dimethylformamide, and dimethylsulphoxide.

If desired, a substituent on a compound prepared according to the foregoing pro-

cess may be converted to another substituent falling within the defined substituents in formula I. These conversions are carried out by methods well known *per se*. Thus, for example, a hydroxyalkyl substituent may be converted to a halogenoalkyl substituent by reaction with a halogenating agent such as thionyl chloride, phosphorus tribromide in the presence of an inert solvent such as chloroform. An alkoxycarbonyl substituent may be converted to a hydrogen atom by the action of heat under basic conditions. A hydroxyalkyl substituent may be converted to an acyloxyalkyl substituent by action of a suitable acylating agent usually at elevated temperatures.

An unsubstituted imino group, for example in a piperazinyl group, may be alkylated or acylated using conventional means such as by reaction with an alkylating or acylating agent for example an alkyl or acyl halide. Similarly the replacement of the imino hydrogen with an alkoxycarbonylalkyl group may be accomplished by reaction with an  $\alpha$ -halogeno alkanonic ester.

It will be clear to those skilled in the art that other substituents may likewise be converted and accordingly a feature of the process of the present invention includes the optional conversion by methods known *per se* of a substituent on the compound produced by reacting compounds of formulae II and III to another substituent falling within the definition of substituents on compounds of formula I.

The compounds produced by the foregoing process may be isolated either *per se* or as acid addition salts or quaternary ammonium derivatives thereof.

The acid addition salts are preferably the pharmaceutically acceptable, non-toxic addition salts with suitable acids, such as those with inorganic acids, for example hydrochloric, hydrobromic, nitric, sulphuric or phosphoric acids, or with organic acids, such as organic carboxylic acids, for example, glycollic, maleic, hydroxymaleic, malic, tartaric, citric, salicylic, *o*-acetoxybenzoic, nicotinic or isonicotinic acid, or organic sulphonic acids for example methane sulphonic, ethane sulphonic, 2-hydroxyethane sulphonic, toluene-*p*-sulphonic, or naphthalene-2-sulphonic acid. Apart from pharmaceutically acceptable acid addition salts, other salts are also included within the scope of acid addition salts such as, for example, those with picric or oxalic acid; they may serve as intermediates in the purification of the compounds or in the preparation of other, for example, pharmaceutically acceptable, acid addition salts, or are useful for identification, characterization or purification of the bases.

A resulting acid addition salt may be converted into the free compound according

to known methods, for example, by treating it with a base, such as with a metal hydroxide or alkoxide, for example an alkali metal or alkaline earth metal hydroxide, for example, lithium hydroxide, sodium hydroxide, potassium hydroxide or calcium hydroxide; with a metal carbonate, such as an alkali metal or an alkaline earth metal carbonate or hydrogen carbonate, for example, sodium potassium or calcium carbonate or hydrogen carbonate; with ammonia; or with a hydroxyl ion exchange preparation, or with any other suitable reagent.

A resulting acid addition salt may also be converted into another acid addition salt according to known methods; for example, a salt with an inorganic acid may be treated with a metal salt, for example a sodium, barium or silver salt, of an acid in a suitable diluent, in which a resulting inorganic salt is insoluble and is thus removed from the reaction medium. An acid addition salt may also be converted into another acid addition salt by treatment with an anion exchange preparation.

Quarternary ammonium derivatives of the compounds of this invention are particularly those formed by reaction with lower alkyl halides, for example, methyl, ethyl, or propyl chloride, bromide or iodide; di-lower alkyl sulphates, for example, dimethyl or diethyl sulphate; lower alkyl lower alkane sulphonates, for example, methyl or ethyl methane sulphonate or ethane sulphonate; lower alkyl aryl sulphonates, for example methyl or ethyl p-toluene sulphonates; and phenyl-lower alkyl halides, for example benzyl or phenethyl chloride, bromide or iodide. Also included are the quaternary ammonium hydroxides and the quaternary ammonium compounds having as anions those of other inorganic or organic acids, for example those of the acids used for the preparation of the previously-mentioned acid addition salts.

The compounds of the present invention possess useful pharmacological properties. Such properties include anti-inflammatory activity and in particular anti-rheumatic activity. Certain of the compounds of formula I also appear to produce an immunosuppressive effect in the animal body.

In the method aspect of the invention, there is provided a method of treating inflammation in non-human animals comprising administering to said animals an amount effective to reduce inflammation of a phthalazine derivative as hereinbefore defined or an acid addition salt or quaternary ammonium derivative thereof.

In the composition aspect of the invention there are provided pharmaceutical formulations in which form the active compounds of the invention will normally be utilised. Such formulations are prepared in a manner well known in the pharmaceutical

art and usually comprise at least one active compound of the invention in admixture or otherwise in association with a pharmaceutically acceptable carrier therefor. For making these formulations the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed or encapsulated in a capsule, sachet, cachet, paper or other container. A carrier or diluent may be solid semi-solid or liquid material which serves as a vehicle, excipient or medium for the active ingredient. Some examples of such diluents or carriers are lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, liquid paraffin, cocoa butter, oil of theobroma, alginates, tragacanth, gelatin, syrup B.P., methyl cellulose, polyoxyethylene sorbitan monolaurate, methyl- and propyl-hydroxybenzoate, talc, magnesium stearate or mineral oil.

The formulations of the invention may be adapted for enteral or parenteral use and may be administered to a subject requiring treatment, for example an animal suffering from an inflammatory condition, in the form for example tablets, capsules, suppositories, solutions or suspensions. The dosage required for the treatment of any animal will usually fall within the range of 0.01 to 250 mg/kg. For example in the treatment of adult humans, each dosage of active ingredient will normally be from 0.01 to 15 mg/Kg, whereas in the treatment of test animals such as mice and rabbits a dosage of 10 to 200 mg/Kg may be used. The formulations of the invention may therefore be provided in dosage unit form, preferably each dosage unit containing from 1 to 1000 mg., more advantageously from 5 to 500 mg., and most preferably from 10 to 250 mg. of the active ingredient of the invention.

The following Examples will further illustrate the preparation of the novel compounds of this invention:—

#### Example 1

1 - Chloro - 4 - phenylphthalazine (10 g.) and N - methylpiperazine (8.5 g.) in dry benzene (40 ml) were heated under reflux for 5½ hours. The solvent was evaporated off and the residue treated with water. This product was extracted with chloroform and removal of the solvent provided the crude base. On recrystallisation from benzene/light petroleum (b.p. 40—50°C), 1 - (4' - methyl - 1' - piperazinyl) - 4 - phenyl - phthalazine, m.p. 160—2°C (9.1 g. 72%) was obtained.

#### Example 2

1 - Chloro - 4 - phenylphthalazine (48.1 g.) and N - (2 - hydroxyethyl) piperazine (52 g.) in dry dioxan (200 ml.) were heated under reflux for 3 hours. The solvent was

- evaporated off under reduced pressure and water was added to the residue. The product was extracted with chloroform, removal of the solvent gave the crude base, and recrystallisation from methanol provided crystals of 1 - [4' - (3'' - hydroxyethyl)-piperazin - 1' - yl] - 4 - phenylphthalazine m.p. 223—5°C (53 g. 79%).

### Example 3

- 10 To N - ethoxycarbonylpiperazine (17 g.) in dry dioxan (50 ml.) was added 1 - chloro - 4 - phenyl phthalazine (12.8 g.) and the solution heated under reflux for 2 hours. The solvent was then removed under reduced pressure and the residue treated with water and extracted with chloroform. The chloroform was removed under reduced pressure and the gummy residue granulated under light petroleum (b.p. 40—60°C) to provide a crude product. Recrystallisation from isopropanol (130 ml.) gave 1 - (4' - ethoxycarbonylpiperazin - 1' - yl) - 4 - phenylphthalazine, m.p. 144—6°C (12.7 g., 66%).

### Example 4

- 1 - Chloro - 4 - phenylphthalazine (16 g.) and N - aminopropyl morpholine (23 g.) in dry dioxan (65 ml.) were heated under reflux for 2½ hours. The solvent was then distilled off under reduced pressure and water was added to the residue. The product obtained via extraction with chloroform was granulated under light petroleum to give the crude amine. Recrystallisation from ethyl acetate (150 ml.) provided 1 - [(3' - morpholino-propyl)amino] - 4 - phenyl phthalazine, m.p. 127°C (18 g., 78%).

### Example 5

- 40 A solution of 1 - chloro - 4 - (p - chloro-phenyl)phthalazine (13.7 g.) and N - (β - hydroxyethyl)piperazine (13 g.) in dry dioxan (70 ml.) was heated under reflux with stirring for 3 hours. After cooling, the solution was poured into water (500 ml.) and the resulting precipitate was filtered off, washed with water, dried and recrystallised from methanol to yield 1 - (4' - β - hydroxyethyl-piperazine - 1' - yl) - 4 - (p - chloro-phenyl)phthalazine, m.p. 210—2°C. (12.2 g., 64%).

### Example 6

- 1 - Chloro - 4 - phenylphthalazine (16 g.) and piperidine (13.5 g.) in dry dioxan (60 ml.) were heated under reflux for 2 hours. After standing overnight, the solvent was evaporated off under reduced pressure and water (600 ml.) was added to the residue. The solids were filtered off, washed well with water, and dried in a vacuum desiccator. The crude product was recrystallised from

methanol to yield 1 - (piperidin - 1' - yl) - 4 - phenylphthalazine (10.5 g. 55%) m.p. 158—9°C. A further crop (2.8 g.) m.p. 158—9°C was obtained from the mother liquors.

### Example 7

By methods similar to those described above, the following compounds were prepared:—

- 1 - (pyrrolidin - 1' - yl) - 4 - phenylphthalazine, m.p. 116—8°C (yield 55%) 70  
1 - (4' - o - tolylpiperazine - 1' - yl) - 4 - phenylphthalazine, m.p. 204—5°C (yield 80%).  
1 - [4' - [1'' - (1''' - β - hydroxyethyl-piperidin - 4''' - yl)prop - 3'' - yl]-piperidin 1' - yl] - 4 - phenylphthalazine, m.p. 133—7°C (yield 66%). 75  
1 - (4' - β - hydroxyethylpiperidiny) - 4 - phenylphthalazine, m.p. 185—7°C (yield 68%). 80  
1 - (4' - β - hydroxyethylpiperazin - 1' - yl) - 4 - benzylphthalazine, m.p. 145—6°C  
1 - (4' - acetylmethylpiperazin - 1' - yl) - 4 - phenylphthalazine, m.p. 162—4°C. 85  
1 - (4' - β - hydroxypropylpiperazin - 1' - yl) - 4 - phenylphthalazine hydrate, m.p. 89—90°C (yield 61%).  
1 - (morpholin - 1' - yl) - 4 - phenylphthalazine, m.p. 193—5°C (yield 39%). 90  
1 - cyclopropylamino - 4 - phenylphthalazine, m.p. 195—6°C.  
1 - cyclopentylamino - 4 - phenylphthalazine, m.p. 192—3°C. 95  
1 - cyclopropylamino - 4 - p - chlorophenylphthalazine, m.p. 190—2°C.  
1 - cyclopropylamino - 4 - benzylphthalazine, m.p. 151—3°C.  
1 - cyclohexylamino - 4 - phenylphthalazine, m.p. 300—3°C. 100  
1 - (4' - phenylpiperazin - 1' - yl) - 4 - phenylphthalazine, m.p. 218—20°C.  
1 - (4' - β - hydroxyethylpiperazin - 1' - yl) - 4 - phenyl - 7 - chlorophthalazine, m.p. 176—7°C. 105  
1 - (4' - β - hydroxyethylpiperazin - 1' - yl) - 4 - (3' - chloro - 4' - methyl-phenyl) phthalazine, m.p. 140—2°C.  
1 - (4' - β - hydroxyethylpiperazin - 1' - yl) - 4 - (2' - methoxyphenyl)phthalazine hydrate, m.p. ca. 100°C. 110  
1 - (4' - β - hydroxyethylpiperazin - 1' - yl) - 4 - (4' - cyclophenyl)phthalazine, m.p. 221—2°C. 115  
1 - (4' - acetyl piperazin - 1' - yl) - 4 - phenylphthalazine monohydrate, m.p. 125°C (with effervescence).  
1 - (4' - β - hydroxyethylpiperazin - 1' - yl) - 4 - (4' - methylthiophenyl) phthalazine, m.p. 162—3°C. 120  
1 - (2' - morpholinoethylamino) - 4 - phenylphthalazine, m.p. 138—9°C. (yield 50%).

1 - (4' -  $\beta$  - hydroxyethylpiperazin - 1' - yl) - 4 - (4' - methoxyphenyl)phthalazine, m.p. 161—3°C (yield 69%).

5 1 - [4' - (pyrrolidin - 1'' - yl) - piperidin - 1' - yl] - 4 - phenylphthalazine, m.p. 157—8°C. (yield 35%).

10 1 - (4' - methylpiperidin - 1 - yl) - 4 - phenylphthalazine, m.p. 143—4°C (yield 54%).

#### Example 8

To a stirred solution of 1 - [4' -  $\beta$  - hydroxyethyl piperazin - 1' - yl] - 4 - phenyl phthalazine (16.7 g.) in dry dioxan (250 ml.) was added slowly acetyl chloride (7.9 g.); after completion of the addition the mixture was heated under reflux for 2½ hours. The product was filtered cold and the solids (ca. 20.7 g. m.p. 234—7°) dissolved in water (100 ml.) and basified with aqueous sodium bicarbonate solution. The precipitated solids were extracted with chloroform and the combined extracts washed and dried (MgSO<sub>4</sub>). The solvent was evaporated off to provide the crude acetate as a yellow solid m.p. 105—7°C (17 g. ca. 90%). Recrystallization from ethyl acetate/light petroleum (b.p. 40—60°C) provided 1 - [4' - (2'' - acetoxyethyl)piperazin - 1' - yl] - 4 - phenylphthalazine, m.p. 110—112°C.

#### Example 9

1 - (4' - Ethoxycarbonylpiperazine - 1' - yl) - 4 - phenyl phthalate (16.3 g.) was added to an aqueous alcoholic sodium hydroxide solution prepared by dissolving sodium hydroxide (5.5 g.) in water (5.5 ml.) and diluting with alcohol (50 ml.), and the mixture heated under reflux for two hours. The cold mixture was acidified with dilute acetic acid, concentrated to small volume and then treated with excess water. The product was filtered, and the filtrate basified with dilute ammonium hydroxide solution. The precipitate was filtered off, washed with water and dried to yield the crude amine. Recrystallization from aqueous alcohol provided 1 - (piperazin - 1' - yl) - 4 - phenylphthalazine monohydrate, m.p. 176—8°C.

#### Example 10

50 1 - (Piperazin - 1' - yl) - 4 - phenylphthalazine monohydrate (10.7 g.) was dehydrated by azeotrope with chloroform in a water separator and after evaporation of the solvent, dry dimethylformamide (100 ml.) was added to the residual anhydrous amine followed by powdered anhydrous potassium carbonate (4.8 g. 2 equivs.). To the stirred suspensions at room temperature was added slowly methyl chloroacetate (4.15 g.) and then the mixture was heated on a steam bath with stirring for 1½ hours. The solvent was partially removed under reduced pressure, the product treated with excess water and was then extracted with chloro-

form. The solvent was evaporated off and the residual gum washed with light petroleum (b.p. 40—60°C). Recrystallization from ethyl acetate/light petroleum (b.p. 40—60°C) gave fine needles of methyl[4' - (4'' - phenylphthalazine - 1'' - yl)piperazin - 1' - yl]acetate, m.p. 140—1°C. (6.8 g. 55%). Similarly the corresponding benzyl acetate was prepared as its monohydrate, m.p. 78—80°C (softens 73°C).

#### Example 11

By the method of Example 10 using allyl bromide in place of methylchloroacetate, 1 - (4' - allyl - 1' - piperaziny) - 4 - phenylphthalazine, m.p. 156—7°C. was obtained.

In the following examples of pharmaceutical compositions, the term "medicament" is used to indicate the compound 1 - (4' -  $\beta$  - hydroxyethylpiperazin - 1' - yl) - 4 - phenylphthalazine. That compound may of course be replaced in these compositions by any other compound of the invention and the amount of medicament may be increased or decreased as is well known in the art depending on the degree of activity of the medicament used.

#### Example 12

##### Tablet formulation

	mg/tablet	
Medicament	15	95
Lactose	86	
Maize Starch (dried)	45.5	
Gelatin	2.5	
Magnesium stearate	1.0	

The medicament was powdered and passed through a B.S. No. 100 sieve and well mixed with the lactose and 30 mg. of the maize starch, both passed through a B.S. No. 44 sieve.

The mixed powders were massed with a warm gelatin solution prepared by stirring the gelatin in water and heating to form a 10% w/w solution. The mass was granulated by passing through a B.S. No. 12 sieve and the moist granules dried at 40°C.

The dried granules were re-granulated by passing through a B.S. No. 14 sieve and the balance of the starch sieved 44 mesh and the magnesium stearate sieved 60 mesh were added and thoroughly mixed.

The granules were compressed to produce tablets each weighing 150 mg.

#### Example 13

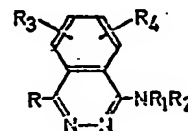
##### Tablet formulation

	mg/Tablet	
Medicament	100	120
Lactose	39	
Maize starch (dried)	80	
Gelatin	4.0	
Magnesium stearate	2.0	125

The method of preparation is identical with that of Example 12 except that 60 mg. of starch is used in the granulation process and 20 mg. during tableting.

# WHAT WE CLAIM IS:—

1. Phthalazines having the general formula



Example 14	
Capsule formulation	
Medicament	mg/Capsule
Lactose	250
	150

10 The medicament and lactose were passed through a No. 44 B.S. sieve and the powders well mixed together before filling into hard gelatin capsules of suitable size, so that each capsule contained 400 mg. of mixed powders.

Example 15	
Suppositories	
Medicament	mg/Suppository
Oil of Theobroma	50
	950

20 The medicament was powdered and passed through a B.S. No. 100 sieve and triturated with molten oil of Theobroma at 45°C to form a smooth suspension.

25 The mixture was well stirred and poured into moulds, each of nominal 1 G. capacity, to produce suppositories.

Example 16	
Cachets	
Medicament	mg/Cachet
Lactose	100
	400

30 The medicament was passed through a B.S. No. 40 mesh sieve, mixed with lactose previously sieved 44 mesh and filled into cachets of suitable size so that each contained 500 mg.

Example 17	
Intramuscular Injection (Suspension in aqueous vehicle)	
Medicament	10 mg.
Sodium Citrate	5.7 mg.
Sodium carboxymethylcellulose (low viscosity grade)	2.0 mg.
Methyl para-hydroxybenzoate	1.5 mg.
Propyl para-hydroxybenzoate	0.2 mg.
Water for Injection to	1.0 ml.

40 The sodium citrate and sodium carboxymethylcellulose were mixed with sufficient water for Injection at 80°C. The mixture was cooled to 50°C and the methyl and propyl parahydroxybenzoates added followed by the medicament previously milled and sieved 300 mesh. When cool the Injection was made up to volume and sterilized by heating in an autoclave.

and acid addition salts and quaternary ammonium derivatives thereof wherein

R represents aryl or aralkyl

R<sub>1</sub> and R<sub>2</sub>, which may be the same or different, represent hydrogen; cycloalkyl; or cycloalkyl alkyl; provided that both R<sub>1</sub> and R<sub>2</sub> are not hydrogen; or

R<sub>1</sub> and R<sub>2</sub> separately represent the same or different heterocyclic or heterocyclic-alkyl or, together with the adjacent nitrogen, represent heterocyclic, the said heterocyclic groups being rings of 5 to 7 atoms at least one of which atoms is carbon, and at least one and optionally up to four of which atoms are hetero atoms selected from nitrogen, oxygen or sulphur; and

R<sub>3</sub> and R<sub>4</sub>, which may be the same or different, represent hydrogen; halogen; cyano; hydroxy; nitro; amino; alkylamino; carboxy; carboxyamido; alkyl; alkylcarbonyl; alkoxy; alkoxy-carbonyl; hydroxy alkyl; halogenoalkyl; or alkyl- or aryl-thio, -sulphinyl or -sulphonyl, the said heterocyclic rings being optionally substituted by alkyl; hydroxyalkyl; halogenoalkyl; aryl; aralkyl; carboxylalkyl; alkoxy- or aralkoxy-alkyl; alkoxy- or aralkoxy-carbonyl; alkoxy- or aralkoxy-carbonylalkyl; alkyl- or aryl-sulphonyloxyalkyl; aminoalkyl; alkylamino-alkyl; acyl; acyl- or acyloxy-alkyl; or by a further heterocyclic or heterocyclic-alkyl group, the heterocyclic rings of which have 5 to 7 atoms, one or two of which are hetero-atoms selected from nitrogen, oxygen or sulphur and the remainder of which ring atoms are carbon, which rings are themselves optionally substituted by alkyl, hydroxyalkyl or halogenoalkyl, the terms alkyl and aryl being as hereinbefore defined.

2. Phthalazines as claimed in Claim 1, wherein

R represents phenyl or phenyl-lower alkyl (the phenyl or phenyl moiety of which is optionally substituted by halogen; cyano; hydroxy; nitro; amino; lower alkylamino; lower alkyl; lower alkylcarbonyl; lower alkoxy; lower alkoxy-carbonyl; hydroxy lower alkyl; halogeno lower alkyl; or lower alkyl-thio, -sulphinyl or -sulphonyl);

R<sub>3</sub> and R<sub>4</sub>, which may be the same or different, represent hydrogen; halogen; cyano; hydroxy; nitro; amino; lower alkyl-amino; lower alkyl; lower alkylcarbonyl; lower alkoxy; lower alkoxy-carbonyl; hydroxy

lower alkyl; halogeno lower alkyl; or lower alkyl-thio, -sulphinyl or -sulphonyl;

R<sub>1</sub> represents hydrogen;

- 5 R<sub>2</sub> represents cycloalkyl or cycloalkyl-moiety of which has 3 to 6 carbons; or heterocyclic or heterocyclic-lower alkyl; or

- 10 R<sub>1</sub> and R<sub>2</sub>, together with the adjacent nitrogen, represent a heterocyclic ring; the heterocyclic rings represented by R<sub>2</sub>, or R<sub>1</sub> and R<sub>2</sub> together, having from 5 to 6 ring atoms, at least one of which is carbon and at least one, and optionally up to 4, of which atoms are hetero atoms selected from
- 15 nitrogen, oxygen or sulphur, which heterocyclic rings are optionally substituted by lower alkyl; hydroxy- or halogeno-lower alkyl; phenyl; phenyl(lower) alkyl; carbonyl(lower)alkyl; lower alkoxy- or
- 20 phenyl(lower)alkoxy-lower alkyl; lower alkoxy-carbonyl or -carbonyl(lower) alkyl; lower alkyl- or phenyl-sulphonyloxy(lower) alkyl; amino(lower)alkyl; lower alkylamino-(lower)alkyl; lower acyl; lower alkylamino-acyloxy-lower alkyl; or by a further heterocyclic or heterocyclic-lower alkyl group, the further heterocyclic rings having from 5 to
- 25 6 ring atoms, one or two of which are hetero atoms selected from nitrogen, oxygen or sulphur and the remainder of which ring atoms are carbon, which further rings are optionally substituted by lower alkyl, hydroxy- or halogeno-lower alkyl, the phenyl substituents or the phenyl moiety of substituents on the
- 30 aforementioned heterocyclic rings being optionally substituted by halogen, cyano, hydroxy, amino, lower alkylamino, lower alkyl or lower alkoxy.

3. Phthalazines as claimed in Claim 2, wherein

R<sub>3</sub> and R<sub>4</sub>, which may be the same or different, represent hydrogen or halogen;

- 45 R represents phenyl or benzyl, the phenyl or phenyl moiety of which is optionally substituted by halogen, cyano, hydroxy, amino, alkylamino, alkyl, alkoxy or alkylthio (the alkyl or alkoxy moieties of which groups have 1 to 4 carbons); and either

- 50 R<sub>1</sub> represents hydrogen and R<sub>2</sub> represents cycloalkyl of 3 to 6 carbons, heterocyclic or heterocyclic-lower alkyl, or

R<sub>1</sub> and R<sub>2</sub>, together with the adjacent nitrogen, represent a heterocyclic ring;

- 55 the heterocyclic rings of R<sub>2</sub>, or R<sub>1</sub> and R<sub>2</sub> together, having from 5 to 6 ring atoms up to two of which are nitrogen, up to one of which is oxygen, and the remainder of which are carbon, which heterocyclic rings are optionally substituted by alkyl, hydroxyalkyl or halogenoalkyl of 1 to 4 carbons; phenyl or benzyl; methoxy- or ethoxy-carbonyl, -carbonmethyl or -carbonyl ethyl; acetyl, or propionyl; acetyl-, propionyl; acetyloxy- or propionyloxymethyl or -ethyl; or by a further
- 60 heterocyclic or heterocyclicmethyl, ethyl,

propyl or butyl, the further heterocyclic rings having from 5 to 6 ring atoms, up to two of which are nitrogen, up to one of which is oxygen and the remainder of which are carbon, which further rings are optionally substituted by alkyl, hydroxyalkyl or halogenoalkyl of 1 to 4 carbons, the phenyl substituents or the phenyl moiety of substituents on the heterocyclic rings being optionally substituted by halogen; hydroxy; methyl; ethyl; methoxy or ethoxy.

4. Phthalazines as claimed in Claim 3, wherein R<sub>3</sub> and R<sub>4</sub>, which may be the same or different, represent hydrogen or chlorine; R represents phenyl or benzyl, the phenyl or phenyl moiety of which is optionally substituted by one or more of methyl, chlorine, cyano methoxy or methylthio; and either

R<sub>1</sub> represents hydrogen and R<sub>2</sub> represents cyclopropyl, cyclopentyl, cyclohexyl, 2-morpholinoethyl or 3-morpholinopropyl, or R<sub>1</sub> and R<sub>2</sub>, together with the adjacent nitrogen, represent piperidin - 1 - yl, pyrrolidin - 1 - yl, morpholin - 4 - yl, 4-methylpiperidin - 1 - yl, 4-β-hydroxyethylpiperidin - 1 - yl, 4-(pyrrolidin - 1' - yl)piperidin - 1 - yl, 4-[1' - (1'' - β - hydroxyethyl)piperidin - 4'' - yl]prop - 3' - yl]piperidin - 1 - yl, or a 4 - X substituted piperazin - 1 - yl group wherein X represents hydrogen, ethoxycarbonyl, methyl, allyl, β - hydroxyethyl, β - hydroxypropyl, phenyl, o - tolyl, acetyl, acetyloxyethyl, methoxycarbonylmethyl, acetylmethyl or benzyloxycarbonyl methyl.

5. 1 - (4' - Methyl - 1' - piperazinyl) - 4 - phenyl - phthalazine.

6. 1 - [4' - (β'' - Hydroxyethyl)piperazin - 1' - yl] - 4 - phenylphthalazine.

7. 1 - (4' - ethoxycarbonylpiperazin - 1' - yl) - 4 - phenylphthalazine.

8. 1 - [(3' - Morpholinopropyl)amino] - 4 - phenylphthalazine.

9. 1 - (4' - β - Hydroxyethylpiperazine - 1' - yl) - 4 - (p - chlorophenyl) phthalazine.

10. 1 - (Piperidin - 1' - yl) - 4 - phenylphthalazine.

11. 1 - (Pyrrolidin - 1' - yl) - 4 - phenylphthalazine.

12. 1 - (4' - o - Tolylpiperazin - 1' - yl) - 4 - phenylphthalazine.

13. 1 - [4' - [1'' - (1''' - β - Hydroxyethylpiperidin - 4''' - yl)prop - 3'' - yl]piperidin - 1' - yl] - 4 - phenylphthalazine.

14. 1 - (4' - β - Hydroxyethylpiperidinyl) - 4 - phenylphthalazine.

15. 1 - (4' - β - Hydroxyethylpiperazin - 1' - yl) - 4 - benzylphthalazine.

16. 1 - (4' - β - Hydroxypropylpiperazin - 1' - yl) - 4 - phenylphthalazine.

17. 1 - (Morpholin - 4' - yl) - 4 - phenylphthalazine.

18. 1 - Cyclopropylamino - 4 - phenylphthalazine.

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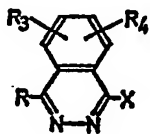
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19. 1 - (4' -  $\beta$  - Hydroxyethylpiperazin - 1' - yl) - 4 - phenyl - 7 - chlorophthalazine.
20. 1 - (4' -  $\beta$  - Hydroxyethylpiperazin - 1' - yl) - 4 - (3' - chloro - 4' - methylphenyl)phthalazine.
21. 1 - (4' -  $\beta$  - Hydroxyethylpiperazin - 1' - yl) - 4 - (2' - methoxyphenyl)phthalazine.
22. 1 - (4' -  $\beta$  - Hydroxyethylpiperazin - 1' - yl) - 4 - (4' - cyanophenyl)phthalazine.
23. 1 - (4' - Acetylpipezazin - 1' - yl) - 4 - phenylphthalazine.
24. 1 - (4' -  $\beta$  - Hydroxyethylpiperazin - 1' - yl) - 4 - (4' - methylthiophenyl)phthalazine.
25. 1 - (2' - Morpholinoethylamino) - 4 - phenylphthalazine.
26. 1 - (4' -  $\beta$  - Hydroxyethylpiperazin - 1' - yl) - 4 - (4' - methoxyphenyl)phthalazine.
27. 1 - [4' - (Pyrrolidin - 1'' - yl) - piperidin - 1' - yl] - 4 - phenylphthalazine.
28. 1 - (4' - Methylpiperidin - 1 - yl) - 4 - phenylphthalazine.
29. 1 - (4' - (2'' - Acetoxyethyl)piperazin - 1' - yl) - 4 - phenylphthalazine.
30. 1 - (Piperazin - 1' - yl) - 4 - phenylphthalazine.
31. Methyl[4' - (4'' - phenylphthalazine - 1'' - yl)piperazin - 1' - yl]acetate.
32. Benzyl[4' - (4'' - phenylphthalazine - 1'' - yl)piperazin - 1' - yl]acetate.
33. 1 - (4' - Allyl - 1' - piperazinyl) - 4 - phenylphthalazine.
34. 1 - (4' - Acetylmethylpiperazin - 1' - yl) - 4 - phenylphthalazine.
35. Pharmaceutically acceptable acid addition salts and quaternary ammonium derivatives of any one of the compounds claimed in Claim 1.
36. Process for preparing a phthalazine as claimed in any one of Claims 1 to 35, which comprises reacting a compound of the formula:—



II

- wherein R, R<sub>3</sub> and R<sub>4</sub> are as defined in Claim 1 and X represents halogen, or alkyl- or aryl-thio, -sulphinyl or -sulphonyl; with an amine, or an acid addition salt thereof, of the formula:—



III

- wherein R<sub>1</sub> and R<sub>2</sub> are as defined in Claim 1, and thereafter optionally converting by methods known *per se* a substituent of a resultant product to another substituent falling within the definitions of R, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> or R<sub>4</sub> given in Claim 1, the resultant compounds of formula 1 being isolated either *per se* or as acid addition salts or quaternary ammonium derivatives.
37. Process as claimed in Claim 36 wherein the reaction is carried out at elevated temperature.
38. Process as claimed in Claim 36 or Claim 37 wherein the reaction is carried out in a solvent and at the reflux temperature of the reaction mixture.
39. Process as claimed in Claim 38, wherein the solvent is selected from benzene, chloroform, toluene, acetone, dioxan, dimethylformamide, or dimethylsulphoxide.
40. Process for preparing a phthalazine derivative, substantially as described in any one of Examples 1 to 6 and 8 to 11.
41. Phthalazine derivative whenever prepared by a process as claimed in any one of Claims 36 to 40.
42. Pharmaceutical compositions comprising as an active ingredient a phthalazine derivative as claimed in Claim 1 or a pharmaceutically acceptable acid addition salt or quaternary ammonium derivative thereof, in association with a pharmaceutically acceptable carrier therefor.
43. A composition as claimed in Claim 42 in the form of a tablet, capsule, suppository, solution or suspension.
44. A composition as claimed in Claim 42 in a dosage unit form containing from 1 to 1000 mg. of said active ingredient.
45. A composition as claimed in Claim 44 containing from 5 to 500 mg. of said active ingredient.
46. A composition as claimed in Claim 45 containing from 10 to 250 mg. of said active ingredient.
47. Pharmaceutical compositions substantially as described in any one of Examples 12 to 17.
48. A method of treating inflammation in non-human animals comprising administering to said animals an amount effective to reduce inflammation of a phthalazine compound as claimed in Claim 1 or a pharmaceutically acceptable acid addition salt or quaternary ammonium derivative thereof.

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